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HIGHLY FUNCTIONALIZED PYRANS DESIGNED FOR MULTIPOINT SIDE CHAIN ATTACHMENT TO THE F-RING SECTOR OF SPONGISTATIN 1 (ALTOHYRTIN A)†

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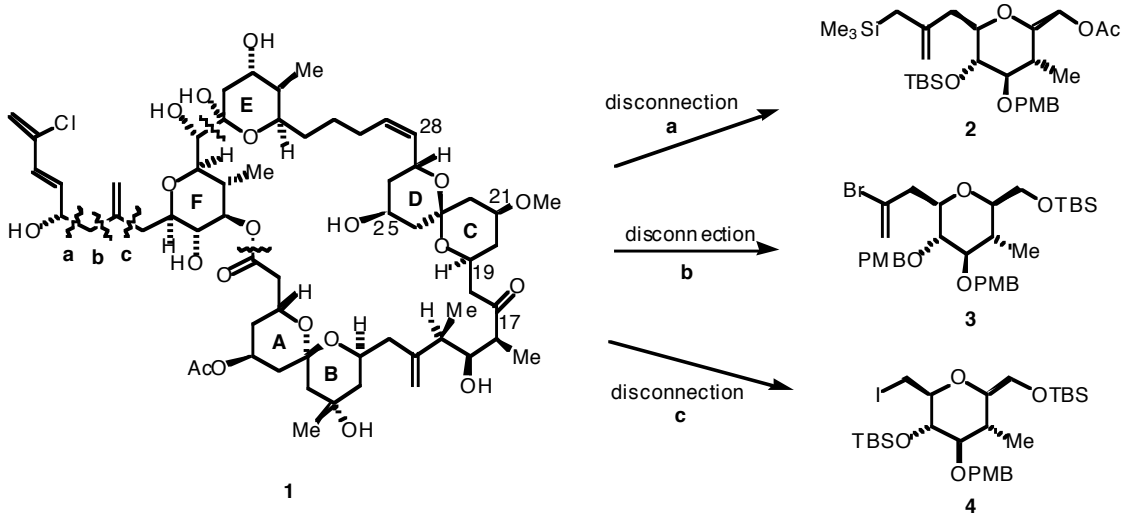
Abstract - The synthesis of three potential F-ring components, variably functionalized for attachment to the chlorodiene side chain by differing chemical means, has been accomplished from D-(+)-mannose as the generic precursor.

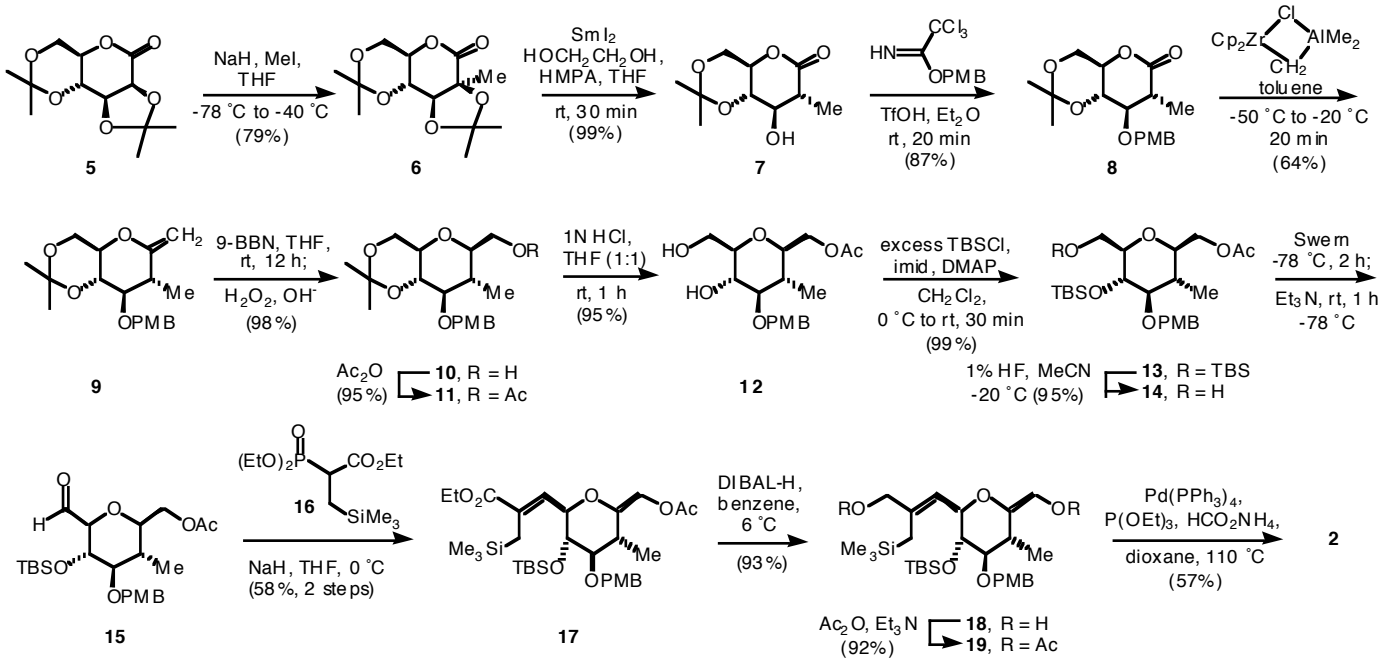
The co-discovery of the spongistatins[1] and altohyrtins[2] has stimulated considerable synthetic interest[3] that has eventuated in four total syntheses.[4-7] Efforts in this laboratory aimed at spongistatin 1 (**1**) have successfully culminated in construction of the complete C1-C28 sector that houses the A/B and C/D spiroacetal subunits.[8] As part of this ongoing investigation, we have more recently pursued the efficient elaboration of ring F in a manner that would allow for connection to the chloro diene side chain via one or more of three bonding modes. In our view, option (**a**) might well be satisfied by synthesis of the allyl silane (**2**), while vinyl bromide (**3**) and the primary iodide (**4**) would potentially qualify for alternatives (**b**) and (**c**). In this communication, we document methodology that provides for accessing all three highly functionalized tetrahydropyran intermediates from D-(+)-mannose.



†This paper is dedicated to Professor Albert I. Meyers, a long-standing friend and scientific compatriot, on the occasion of his 70th birthday.

The synthesis of **2** began with sequential acid-catalyzed two-fold acetalization and Swern oxidation of this carbohydrate to generate **5**[9] (Scheme 1). Direct methylation of the enolate anion of **5** proved to be more facile than expected.[10] The ensuing one-step α-deoxygenation with concurrent liberation of the C3

Scheme 1

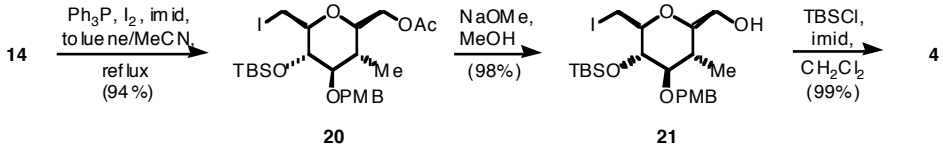


hydroxyl was accomplished with SmI_2 as the electron-transfer agent[11] in quantitative yield. With arrival at **7**, four chiral centers having the proper absolute configuration had already been established. Subsequent PMB protection and Tebbe olefination led efficiently *via* **8** to **9**, which was immediately hydroborated and acetylated in order to preclude possible migration of the double bond internal to the ring. In order to achieve selective protection of the secondary alcohol, **11** was hydrolyzed in 1N hydrochloric acid, disilylated, and subjected to chemoselective Si-O bond cleavage with 1% HF in acetonitrile at -20 °C. Incorporation of the allylsilane function was realized by sequential Swern oxidation and *Z*-selective Horner-Emmons condensation with α-phosphono-β-silylpropionate (**16**).[12] After considerable experimentation, successful reduction with critical 1,2-shift of the double bond was found to be possible by conversion of **17** to acetate (**19**) and heating of this advanced intermediate with $Pd(PPh_3)_4$ and ammonium formate in dioxane at 110 °C. A possible mechanism for this contrathermodynamic transformation has been formulated in a different context.[13]

For the purpose of accessing iodide (**4**), we returned to primary carbinol (**14**) and successfully carried out its efficient conversion to **20** (Scheme 2). Since base-promoted deacetylation to give **21** could be implemented without intramolecular cyclization, the three-step conversion to **4** proved not to be at all problematic.

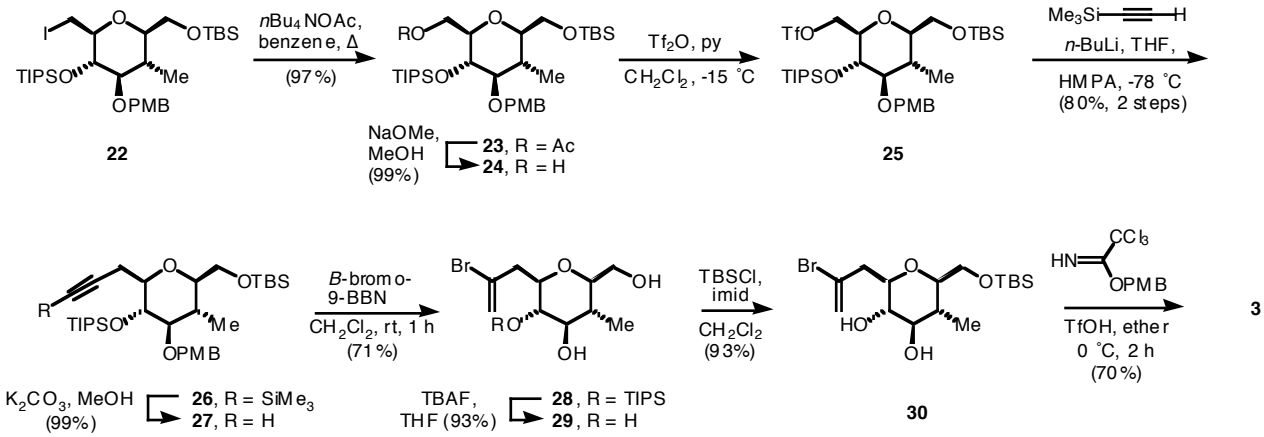
At this point, our efforts were now directed to **3**. From among the possibilities that were investigated,

Scheme 2



iodide (**22**), prepared analogously to **20**, evolved as a utilitarian intermediate (Scheme 3). S_N2 substitution without elimination could be reproducibly accomplished with tetra-*n*-butylammonium acetate in benzene.[14] Subsequent activation as in triflate (**25**) allowed for vastly improved replacement by an

Scheme 3



alkyne fragment as in **26** and **27**. When the latter was exposed to 9-bromo-9-BBN at 0 °C for the purpose of producing a vinyl bromide,[15] the TBS and PMB protecting groups were cleaved as well, thus facilitating arrival at triol (**29**) following treatment with fluoride ion. The latter maneuver was necessary due to an inability to silylate the secondary hydroxyl in **28** because of steric screening by the neighboring TIPS group. In contrast, **30** was doubly protected smoothly in the presence of the PMB trichloroacetimidate reagent under conditions of acid catalysis.

In summary, these studies serve to chart possible directions for the critical incorporation of ring F into spongistatin 1. Several key facets of the investigation include the SmI_2-promoted reduction of **6**, reductive deoxygenation of **19**, and efficient incorporation of the trimethylsilylacetylene group as in **26**.

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